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Girard's Reagent for the Isolation of Carbonyl Compounds*

By JOHN D. CAWLEY

THE term "Girard's reagent" refers in general to a salt of a quaternary ammonium hydrazide whose function it is to form, with carbonyl compounds, hydrazones which are soluble in water and insoluble in nonhydroxylic organic solvents. Solution of these hydrazones in water, and solvent extraction then enable a separation from any water-insoluble contaminants, after which the carbonyl compounds may be regenerated and recovered by simple means.

Girard and Sandulesco (1,2) described as most suited to this function either (carbohydrazidomethyl) trimethylammonium or (carbohydrazidomethyl)pyridinium chlorides, which have the following structures:

$[NH_2NHCOCH_2N(CH_3)_3]^+Cl^-$, and

$[NH_2NHCOCH_2NC_5H_5]^+Cl^-$, and are

known as Reagents T and P, respectively. Both may be readily prepared (3), and both furnish hydrazones rapidly and completely with aldehydes and the majority of ketones. Reagent T is hygroscopic, and it is best to recrystallize an old sample before use; Reagent P requires no special handling, and may be kept for long periods without deterioration. Ketonic hydrazones formed with either reagent are quantitatively hydrolyzed by dilute mineral acid, while aldehydic hydrazones are essentially nonhydrolyzable, so that ketones may be separated not only from noncarbonyl compounds but also from aldehydes.

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Isolation Process

The following directions may be generally applied: The substance in a convenient amount of alcohol containing 10 per cent by volume of acetic acid, accurately measured, is refluxed for one to one and one-half hours with a small excess of the reagent. After cooling, the mixture is poured into sufficient ice and water, containing enough sodium carbonate to neutralize nine tenths of the acetic acid, so that the final concentration of alcohol does not exceed 10 per cent. After ether extraction, the aqueous layer is brought to approximate normality with mineral acid, and after standing three to four hours, the ketone is recovered by ether extraction.

Occasionally, stubborn emulsions are encountered during the first extraction, in which case Girard and Sandulesco then recommend that the alcohol be replaced, after the initial reaction, by ethylene glycol; a volume equal to that of the alcohol is added and the latter

distilled off *in vacuo*. Ether extraction of the glycol solution then proceeds very cleanly, the addition of carbonate being unnecessary. The glycol layer is diluted with four volumes of water, and the ketonic material recovered as above. This modification appears to be little used, but can be highly recommended, especially when working on any considerable scale, since the extraction of cumbersome amounts of solution is avoided.

Although either procedure can be applied with equal success to mixtures in which mere traces of ketones are present or to those in which ketones are the main constituent, the method was developed primarily for the former application, and it has, therefore, been the procedure principally in vogue. Traces of ketonic material have been isolated from various essential oils and biological materials (4,5). The method aided considerably the isolation of the cortical hormones (6), and in Europe has been applied on an industrial scale to the preparation of estrone from urine.

It is evident that, aside from these rather specialized uses, the reagent is of general value in synthetic chemistry; ketonic products may be separated from nonketonic starting materials, and carbonyl reagents or by-products removed from noncarbonyl products. Scattered examples of these applications appear in the literature, typical being the estimation of the amounts of 1,2- and 1,4-addition products formed in the reaction of various Grignard reagents with an α,β-unsaturated ketone (7).

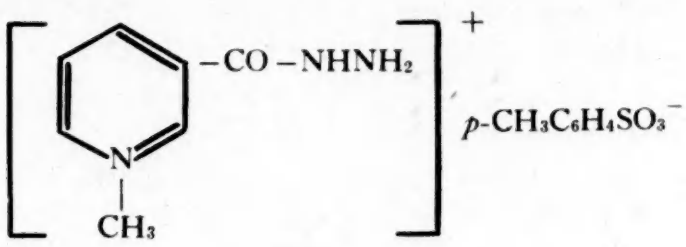
Other Hydrazone Applications

Although the hydrazones formed with Reagents T and P are, in general, crystalline solids, they are seldom used for the identification of carbonyl compounds, since they are hygroscopic and offer no advantages over the more usual reagents. They may, of course, serve for the water-solubilization of lipid-soluble compounds (8).

The hydrazones derived from Reagent T have the property of forming highly insoluble salts with mercuric iodide. In this way Girard and Sandulesco were able to detect the presence of cinnamaldehyde at a concentration of 30 gammas per milliliter. Hughes (9) has also described a quantitative procedure for ketosteroids based on the precipitation of the Reagent T hydrazones with mercuric iodide. For these reactions the use of pure reagent (3) is advisable.

Girard and Sandulesco observed that the rate of hydrazone formation is a function of the structure of the ketone, and arranged various types in the following approximate order of decreasing reactivity: methyl alkyl > alicyclic > methyl aryl > di-aryl. An accumulation of substituents about the carbonyl group also reduces the reaction rate through steric effects. No precise data on these observations have been assembled, and the possibilities of fractionation amongst various ketones can be determined accurately only by further research.

Although the fact that the aldehylic hydrazones formed with Reagents T and P resist hydrolysis may be an advantage in certain cases, it would be desirable to have a reagent which would permit the recovery of aldehydes as well as ketones. Allen and Gates (10) have described such a compound, N-methyl-β-carbo-hydrazinopyridinium *p*-toluenesulfonate,



Well-crystallized hydrazones, suitable for identification purposes, are formed with all but α,β-unsaturated carbonyl compounds, and these are water-soluble and readily decomposed to regenerate the original aldehyde or ketone. This reagent is not too accessible, but its usefulness suggests that other, simpler compounds performing its function may be found.

Evidently the basic principle underlying Girard's reagent can be applied to functions other than the carbonyl group. A step in this direction has recently been taken by Plattner and Geiger (11), who have described the preparation and use of the acid chloride of betaine hydrochloride for the solubilization of alcohols and amines. As yet, however, it does not appear that this method has been placed on as broadly applicable a basis as is the case with Girard's reagent.

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The Oxo Process

By C. F. H. ALLEN*

ONE of the most outstanding recent developments in aliphatic chemistry is the production of aldehydes and ketones from ethylenic hydrocarbons and water gas. This has been called the Oxo process in Germany, which is the source of our published knowledge on this subject.

The chemistry involved appears to be very simple, consisting in the addition of carbon monoxide and hydrogen to the hydrocarbon according to the equations:

$$RCH=CHR + CO + H_2 = RCH_2CHRCHO$$
$$2\,RCH=CHR + CO + H_2 = (RCH_2CHR)_2CO$$

It is stated that, in order to secure aldehydes, it is advantageous to have hydrocarbons terminating in $=CH_2$ predominant in the charging stock.

The products are said to be a mixture of straight-chain aliphatic aldehydes and ketones, the former predominating. For instance, with ethylene, 70% of the product is propionaldehyde and 30% is diethyl ketone. The limits of the reaction have not been announced. It is known that the product from unsaturated hydrocarbons containing from eleven to seventeen carbon atoms was a basic starting material in the German program.

The carbonyl compounds formed in the Oxo process can be converted into other substances by known chemical processes. For example, reduction in the presence of a Raney nickel catalyst gives the corresponding alcohols. The latter can then be sulfated to produce the modern detergents. This series of reactions was utilized for this purpose in Germany, and was probably the main reason for developing of the Oxo process.

The raw materials are water gas and unsaturated hydrocarbon fractions; the latter, if not available as by-products, can be made by a cracking process from higher hydrocarbons, e.g., C_{20} to C_{40}.

General Procedure

The Oxo reaction can be carried out in batches or in a continuous-type reactor; since development is only beginning, many technical difficulties remain to be overcome. The pressures used are of the order of 150 atmospheres, with temperatures up to 180°C. After partial conversion and separation of the oxygenated

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fraction by distillation, the residue is made up with new gas and recirculated.

The catalysts are "standard Fischer-Tropsch material," containing cobalt, thoria, and magnesia, and are deposited in the form of carbonates on Kieselguhr. For use, this material is suspended in Diesel oil. A given lot can be reused fifty to one hundred times, depending on the nature of the hydrocarbon starting material. The catalyst for the Oxo process is not sensitive to sulfur, so the removal of sulfur-containing compounds from the water gas is not necessary. If the carbonyl compounds are later to be reduced to alcohols, a purified hydrogen is essential, since the catalyst for this reaction is sensitive to sulfur. Hence, it is economical to purify the entire gas mixture.

The future possibilities that will result from the development of this process are very great, and are obvious to anyone with even a rudimentary knowledge of organic chemistry. An unlimited source of aliphatic aldehydes, ketones, and related compounds may be anticipated.

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